IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Salvati, *et al.*	Docket No:	373987-004US (396982)
Serial No.:	**10/541,195**	Confirmation No.:	7746
Filed:	June 30, 2005	Group Art Unit:	1617
For:	**ALPHA-AMINOAMIDE DERIVATIVES USEFUL AS ANTIMIGRAINE AGENTS**	Examiner:	JAVANMARD, Sahar

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Giorgio SANDRINI, an Italian citizen residing at Pavia(Italy), p.za del Carmine, 2, hereby declare and state:

1. Given my education and experience, as disclosed in the attached *curriculum vitae*, particularly in the areas of pathogenic mechanisms, the classification and treatment of headache and neuropathic pain, the neurophysiology of pain and the autonomic system, extra-pyramidal disorders and neurorehabilitation, I consider myself a person of at least ordinary skill in the art and am able to provide the following testimony.

2. Migraine and TGN are distinct entities from a clinical, pathogenic and therapeutic point of view.[1]

3. Migraine and TGN are distinct from a clinical point of view. The following clinical features of migraine and TGN illustrate some of the many exemplary differences between the two.[2]

4. The epidemiology of migraines and TGN are quite different. The prevalence of migraine is significantly higher (10%) than TGN (<0.01%). Further, TGN is much more likely to afflict those age 60 and over, whereas migraine is more common in younger persons. Migraines have also been shown to have a hereditary component; TGN does not demonstrate a hereditary component.

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[1] For example, the International Headache Society and the International Association for the Study of Pain categorize these conditions separately. *See The International Classification of Headache Disorders*, 2nd edition. Cephalalgia (2004) 24:1; and Merskey H and Bogduk N. *Classification of chronic pain: Descripnon of chronic pain syndromes and definitions of pain terms*. Seattle: IASP Press, 1994: 59--71.

[2] These differences are outlined in the HIS and IASP classifications, *supra*, and also by Silberstein, *et al.*, *Headache in Clinical Practice*. Oxford: ISIS Medical Media (1998); and Nurmikko TJ and Jensen TS. *Trigeminal Neuralgia and other facial neuralgias*. The Headaches, 3rd edition. Lippincott Williams & Wilkins (2006) Philadelphia (USA).

5. Trigeminal pain is strictly unilateral. Migraines can occur both unilaterally and bilaterally. The *situs* of pain is considered pathognomonic (highly indicative) of TGN. Migraine pain can occur in different sites and pain in any one of these sites is not necessarily indicative of migraine pain.

6. Migraine pain tends to be of a pulsating quality, of moderate to intense severity and can last from 4–72 hours; TGN pain is usually sharp or stabbing, very severe in quality, and usually lasts on the order of minutes. TGN pain demonstrates a refractory period after the initial attack before a subsequent attack and unlike migraine is not aggravated by physical activity. Further, in contrast to migraine where secondary symptoms such as nausea, vomiting, and photo/phonophobia occur, TGN patients usually present with no additional symptoms.

7. TGN pain may be instantly provoked by trivial stimuli such as washing, shaving, smoking, talking and/or brushing the teeth (trigger factors) and frequently occurs spontaneously. Small areas in the nasolabial fold and/or chin may be particularly susceptible to the precipitation of pain (trigger areas). No similar trigger factors can be observed with migraines, in which other precipitating factors are known: stress, food, weather, and menstruation. In contrast to TGN triggers, migraine triggers do not act instantaneously.

8. Migraine suffers usually experience prodomal phenomena (indications that a migraine will soon occur) that are indicative of the involvement of the central nervous system (CNS) in migraine attacks. There are no prodromal symptoms for TGN.

9. While neurophysiological investigations and neuroimaging are considered of limited usefulness in migraine diagnosis and treatment[3], they are mandatory in TGN to exclude secondary conditions such as tumors because of the close similarities between idiopathic and symptomatic TGN.[4]

10. It has been demonstrated that migraine pain may be a form of sterile neurogenic inflammation. Trigeminal sensory C-fibers contain various neuropeptides including substance P, Calcitonin Gene-Related Peptide (CGRP) and neurokinin A. It is generally accepted that antidromic stimulation of the trigeminal nerve releases neuropeptides from the C-fibers, resulting in neurogenic inflammation. Released neuropeptides interact with the blood vessel wall, producing dilatation, plasma extravasation and sterile inflammation.[5]

11. Biochemical markers have been extensively investigated in the blood and spinal fluid of migraine patients.[6] A decrease of opiates and abnormalities in various amine levels have been observed in several studies but they are considered absolutely non-specific indications. Their appearance is attributed to secondary conditions not related to the specific mechanism involved in

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[3] Sandrini, *et al., Neurophysiological tests and neuroimaging procedures in non-acute headache: guidelines and recommendations.* Eur J Neurol. (2004) 11(4):217–24.

[4] *See* the *ICHD* (fn. 1) and Gronseth, *et al., Practice Parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review): report of the quality standards subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies.* Neurology. (2008); 71(15):1183–90.

[5] Silberstein, *et al., Headache in Clinical Practice.* Oxford: ISIS Medical Media, (1998); and Goadsby P. *Pathophysiology of migraine.* Neurol Clin. (2009); 27(2):335–60.

[6] Sarchielli P and Bach FW. *Blood and spinal fluid in migraines.* The Headaches (3rd edition); Lippincot, Philadelphia, (2006): 321–330.

migraine pain. In point of fact, these changes have been observed to occur in non-migraine pain conditions. Likewise, changes in substance P levels in migraine patients is not indicative of substance P having a role in migraine.

12. Substance P levels (from serum or cerebrospinal fluid) are considered a very poor marker of neurogenic inflammation as evidenced by those studies which have found changed substance P levels where neurogenic inflammation has no role.[7] Changes in substance P levels have been observed in other neurological diseases including stroke with depression and psychiatric diseases such as post traumatic stress disorder.[8] Substance P levels are not considered a specific marker of neurogenic inflammation.

13. Therefore, the study of Strittmatter [9] does not support the concept that trigeminovascular activation and neurogenic inflammation play a pathogenic role in TGN, since specific markers of this condition were not evaluated.

14. Vascular and endothelial factors such as endothelin-1, nitric oxide and CGRP are, in contrast, specific to migraine.[10]

15. These mediators interact with the blood vessel wall, producing dilatation, plasma extravasation and sterile inflammation.[11] For example, migraines can be induced using nitric oxide donor administration.[12] Mast cell degranulation has also been shown to be highly specific to migraine attacks.[13] It is noted that extravasation phenomena represent only a part of the phenomena occurring in a migraine attack.

16. Sensitization phenomena, which can include the sequential recruitment of spinal and supraspinal nociceptive neurons, can play a role in the pathophysiology of migraine.[14] Sequential recruitment is consistent with the long lasting nature of migraine pain and confirms the fundamental role of a sensitization phenomena.[15]

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[7] *See, e.g.,* Russell J, and Bieber C. *Myofascial pain and fibromyalgia syndrome.* Wall and Melzack's Textbook of Pain. 5th Edition. London: Elsevier; (2006) p. 669–681.

[8] Li, *et al. Plasma and cerebrospinal fluid substance P in post-stroke patients with depression.* Psychiatry Clin Neurosci. (2009) 63(3):298–304; and Geracioti, *et al. Elevated cerebrospinal fluid substance P concentrations in posttraumatic stress disorder and major depression.* Am J Psychiatry. (2006); 163(4):637–43.

[9] Strittmatter M, *et al. Cerebrospinal Fluid Neuropeptides and Monoaminergic Transmitters In Patients With Trigeminal Neuralgia.* Headache. (1997); 37(4):211-6.

[10] Goadsby P. *Pathophysiology of migraine.* Neurol Clin. (2009); 27(2):335–60.

[11] Silberstein, *et al., Headache in Clinical Practice.* Oxford: ISIS Medical Media, (1998); and Goadsby P. *Pathophysiology of migraine.* Neurol Clin. (2009); 27(2):335–60.

[12] Sances, *et al. Reliability of the nitroglycerin provocative test in the diagnosis of neurovascular headaches.* Cephalalgia. (2004) 24(2):110–9.

[13] Olesen, *et al. Finding new drug targets for the treatment of migraine attacks.* Cephalalgia (2009).

[14] Burstein, *et al. The development of cutaneous allodynia during a migraine attack. Clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine.* Brain (2000) 123: 1703–1709; and Goadsby P. *Pathophysiology of migraine.* Neurol Clin. (2009); 27(2):335–60.

[15] *Id.*

17. There is no evidence that sensitization phenomena play a role in TGN pain. TGN pain is short-lived, which suggests a different pathophysiology for TGN as compared to migraine. TGN pain appears to be a result of changes in nerve excitability.

18. The etiology of TGN and migraine are different. The pathophysiology of migraine involves vascular mechanism which activate a central sensitization phenomena resulting in a long lasting process (4-72 hours).

19. Aethiology of TGN is not well known, but a change in nerve and/or ganglion cell excitability is considered a key mechanism.[16]

20. Demyelination of nerve fibers and/or compression by a blood vessel may be a cause of changes in nerve excitability associated with TGN.[17]

21. Some antiepileptics (carbamazepine in particular) are known to improve pain in TGN, and this activity is considered to be related to an effect on nerve hyperexcitability.

22. Animal models for the mechanistic study of migraine have been proposed.[18]

23. Animal migraine models are based on the neurovascular activation of the pain control system.[19]

24. Animal TGN models, in contrast, are based on chronic lesion of the trigeminal nerve (i.e. chronic constriction of the infraorbital nerve).[20]

25. Patients presenting with migraine or TGN are treated differently from each other. For example, pharmacologic treatment of migraine involves both acute and prophylactic therapy. TGN is treated only with prophylactic therapy.

26. Migraines are first treated with triptans, which block trigeminovascular activation.[21] Triptans target both central[22] and peripheral (in particular, vascular) sensitization phenomena.[23] I am unaware of any controlled studies about the possible effect of triptans on TGN in the literature.

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[16] There are several lines of evidence that support this view. First, imaging performed during posterior fossa surgery for TGN have consistently shown a blood vessel in contact with the nerve root. Second, elimination of the compression leads to long-term pain relief in most patients. Third, intra-operative recordings show immediate improvement in nerve conduction following decompression, fitting with the general experience that patients tend to wake up from the operation pain-free. Fourth, sensory functions recover as well following decompression. *See* Nurmikko TJ and Jensen TS, *supra*.

[17] Nurmikko TJ, Jensen TS. *Trigeminal Neuralgia and other facial neuralgias*. The Headaches, 3rd edition. Lippincott Williams & Wilkins, 2006 – Philadelphia (USA).

[18] Bergerot, *et al. Animal models of migraine: looking at the component parts of a complex disorder*. European Journal of Neuroscience (2006) Vol. 24: 1517–1534, and Greco, *et al., Role of calcitonin gene-related peptide and substance P in different models of pain*. Cephalalgia. (2008); 28(2):114–26.

[19] Bergerot, *et al.* (2006), *supra*.

[20] Christensen, *et al. Effect of gabapentin and lamotrigine on mechanical allodynia-like behavior in a rat model of trigeminal neuropathic pain*. Pain 93 (2001), 147–153; Hao, *et al., Lacosamide, a new antiepilectic, alleviates neuropathic pain-like behaviours in rat models of spinal cord or trigeminal nerve injury*. Eur J Pharmacol (2006) 553; 135–140.

27. According to the most important guidelines, the only drug definitely shown to be effective for controlling pain in patients with TGN is carbamazepine.[24] Only sodium valproate, amitriptyline, propanolol, timolol and methysergide have been included in the guidelines of the American Academy of Neurology[25] for migraine prophylaxis therapy. Recently, also topiramate has been considered to be effective for migraine.[26]

28. It is my conclusion that in the main international guidelines there is no recommended drug for the prophylactic treatment of both migraine and TGN.

29. TGN can be treated surgically by removing nerve compression by a blood vessel.[27] No studies have been performed concerning surgical treatments for migraine.

30. The clinical features of and therapeutic approach to these two diseases are markedly different.

31. I declare further that all statements made in this Declaration of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: September 2, 2009

Giorgio SANDRINI

[21] Silberstein SD. *Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review).* Neurology (2000); 55: 754–763; and Silberstein SD. *Treatment recommendations for migraine.* Nat Clin Pract Neurol. (2008); 4(9):482–9.
[22] Silberstein SD. (2000), *supra.*
[23] Olesen, *et al. Origin of pain in migraine: evidence for peripheral sensitisation.* Lancet Neurol. (2009);8(7):679–90.
[24] Gronseth, *et al.* (2008), *supra.*
[25] Silberstein SD. (2000), *supra.*
[26] Silberstein SD. (2008), *supra.*
[27] Gronseth, *et al.* (2008), *supra.*

CURRICULUM VITAE OF PROFESSOR GIORGIO SANDRINI

Giorgio Sandrini is Full Professor of Neurology and the head of the Department of Neurology and Neurorehabilitation at the Institute of Neurology, "C. Mondino" Foundation (Pavia, Italy) and the University Department of Neurological Sciences (University of Pavia). He is Chief of Pavia Unit I of University Centre for Adaptive Disorders and Headache (UCADH) and Executive Director of UCADH.
He is also the incoming President of the Italian Society of Neurorehabilitation.

He is or was member of the Research Group on Headache and Migraine of the World Federation of Neurology; several International Headache Society (IHS) Subcommittees (classification, Clinical Trials, linguistic, etc.); the Headache Panel of European Federation of Neurological Societies (EFNS); the EFNS Task Force on Neurophysiological Tests and Neuroimaging Procedures in Non-acute Headache (Chairman); the EFNS task force on guidelines on the treatment of the tension-type headache and the Ad-Hoc Expert Group on Migraine and Neuropathic Pain in children/adolescents of the European Medicines Agency (EMEA). He was member of the International Headache Society Council; the International Headache Society Executive Committee; and the Executive Council of Italian Society for the Study of Headache.

He is active member of several societies and of the editorial Board in various scientific journals.

His main fields of interest include pathogenic mechanisms, classification and treatment of headache and neuropathic pain, neurophysiology of pain and autonomic system, extrapyramidal disorders, and neurorehabilitation. His scientific activities include the publication, editing, and co-editing of a large number of articles, congress proceedings and chapters of books. He has also organized numerous national and international scientific congresses. He has participated as an investigator, principal investigator or coordinator to a large number of clinical trials carried out according to the good clinical practice (GCP) on the treatment of headache or neuropathic pain.